THE HARTWELL FOUNDATION

2015 Individual Biomedical Research Award

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Targeting a Gut Sensory Neurocircuit to Modulate Autism Spectrum Disorders

Today, there are no effective drug therapies that address the core symptoms of autism spectrum disorder (ASD). Yet, ASD is a major public health challenge in the U.S. and its prevalence has increased dramatically over the past several decades. In the 1980's, the likelihood of an 8-year old to be diagnosed with ASD was 1 in 2000, whereas, today it is 1 in 68. Early in life, autistic children have trouble socializing, develop repetitive behaviors, and most suffer from gastrointestinal (GI) disturbances. Indeed, over 50% of children diagnosed with ASD suffer from bowel inflammation, pain, constipation, and/or diarrhea. Although such GI disturbances have been linked to behavioral abnormalities in ASD, the biological explanation remains unknown. Gut microbes have been suggested as a possible link, but to influence the behavior they would have to interact first with cells in the lining of the gut, where sensory cells exist (e.g., enteroendocrine cells). It has long been assumed these cells lack contact with nerves and could only communicate outside the gut through the action of hormones. In this regard, Diego has discovered that enteroendocrine cells are capable of converting a stimulus of sugar into an electrical impulse that can excite neurons in the lining of the gut. He observed that such sensory cells connect with the hypothalamus (a region of the brain involved in fear, feeding, fighting, and social interaction) via the vagus nerve (cranial nerve X, which is part of the involuntary nervous system that controls unconscious body functions like heart rate and digestion). On this basis, he hypothesizes that enteroendocrine cells in the gut can directly influence the brain and thus, behavior. To test his theory, he will define alterations in the connectivity of this gut-brain neurocircuit using a mouse model of ASD. His approach will be to manipulate the enteroendocrine cells-brain neurocircuit with the precision of an optogenetic molecular switch, effectively exciting enteroendocrine cells by blue light to modulate ASD-like behaviors. If Diego is successful in identifying an alteration in gut sensory transduction that alters how enteroendocrine cells in the gut influence the brain, it will be possible to translate his findings to develop a targeted drug therapy for children with ASD who suffer from GI disturbances.